Date, author ?

Catechol (CAS no. 120-80-9)
Synonyms: Pyrocatechol, catechin, 1,2-dihydroxybenzene
Amount in cigarette smoke: 40 to 350 microgram/cigarette (Hoffmann et al., 1978)

<u>Bottom line</u>
Earlier experiments showed that **catechol** is an animal co-carcinogen targeting the skin and stomach. More recent experiments showed that catechol is also an animal carcinogen targeting the stomach. It is classified by IARC into Group 2B (possibly carcinogenic to human). It is in the Hoffmann's list as a major co-carcinogenic compound in cigarette smoke and published by the CPSC. The Surgeon General's report also indicated the co-carcinogenic activity of catechol in the cigarette smoke. The MA Department of Health lists catechol in proposed regulations. Catechol belongs to the phenolic antioxidant class. NTP had planned to evaluate this class for carcinogenesis. However, EPA has not classified catechol with respect to potential carcinogenicity and has not reported a cancer potency factor for catechol.

<u>Catechol is classified by IARC into Group 2B (possibly carcinogenic to humans) (IARC, 1999)</u>
The classification was based on animal data, since no case reports or epidemiological studies of cancer in humans were available to the Working Group. The evidence for carcinogenicity of catechol in experimental animals was originally indicated in skin painting studies in mice (Van Duuren et al., 1973; Van Duuren and Golschmidt, 1976). When applied to mouse skin together with a low dose of benzo(a)pyrene, catechol increased the carcinogenic effects of benzo(a)pyrene: the number of skin cancer, i.e., pappiloma and squamous cell carcinomas was increased in mice treated with catechol and benzo(a)pyrene as compared to mice treated with benzo(a)pyrene alone. Therefore, catechol is a co-carcinogen. The co-carcinogenicity of catechol was confirmed in several later experiments in a second species, i.e., rat. Thus, continuous oral treatment of rats with catechol after a single intragastric dose of MNNG strongly enhanced squamous-cell carcinomas of the forestomach and adenocarcinomas of the glandular stomach (Hirose et al., 1988; Yamaguchi et al., 1989). More recent experiments in rats, catechol alone induced adenocarcinomas in the glandular stomach in several strains (Hirose et al., 1990, 1993; Tanaka et al., 1995). IARC evaluated animal data that there is *sufficient evidence* in experimental animals for the carcinogenicity of catechol.

<u>Catechol is in the Hoffmann's list as a co-carcinogen</u>
The finding of Van Duuren et al. (1973) that catechol is a co-carcinogen was confirmed by the Hoffmann's group (Hecht et al., 1975; Melikian et al., 1989). In a review on tobacco carcinogenesis, Hoffmann et al. included catechol in a list of co-carcinogenic agents in tobacco smoke (1978). Subsequently, in the U.S. Consumer Product Safety Commission (CPSC, 1993) the Hoffmann's list indicated that catechol is not a carcinogen but a very effective co-carcinogen in cigarette smoke (Hoffmann 1993). Catechol itself is the most abundant co-carcinogen in cigarette smoke (up to 400 microgram/cigarette).

<u>The report of the Surgeon General included catechol as a co-carcinogen in cigarette smoke</u>
Referring to the Hoffmann's table of co-carcinogens (1978), the report of the Surgeon General on "The health consequences of smoking – the changing cigarette" indicated that based on studies on mouse skin that a selective reduction of tumor initiators and co-carcinogens would lead to a significant reduction of the carcinogenic potential of cigarette smoke (DHHS, 1981).

<u>Catechol is listed in proposed regulations by the MA Department of Health</u>
The proposed regulations require that the amounts of specific constituents in cigarette smoke, which are known or believed to be the cause of morbidity and mortality, to be reported (*www.state.ma.us/dph/mtcp/report/smoktox.htm*).

NTP planned studies of catecholic antioxidant class for carcinogenesis in the fiscal year 1998 annual plan

Many chemicals in the catechol class have antioxidant properties. They are able to prevent autooxidation via inhibition of radical formation, decomposition, or peroxide formation. Synthetic catechol class antioxidants are used in food, e.g., butylated hydroxyanisole (BHA). Catechol class was considered by NTP for evaluation because these chemicals may promote cancer in rodents. Catechols are generally not mutagenic. They may have two different effects. For example, BHA promotes forestomach and urinary bladder cancer in rodents while it inhibits liver and mammary gland cancer in rodents when applied after an initiating dose of another chemical (Ito and Hirose, 1987). (http://ntp-server.niehs.nih.gov/htdocs/98AP/contents.html)

EPA has not classified catechol with respect to potential carcinogenicity

There is no cancer potency factor for catechol reported by U.S. EPA (www.epa.gov/ttnatw01/hlthef/pyrocate.html) and by the California EPA (www.oehha.ca.gov/scientific/otherhtml).

Hydroquinone (CAS no. 123-31-9)
Synonym: 1,4-dihydroxybenzene, benzoquinol
Amount in cigarette smoke: TBD

Resorcinol (CAS No. 108-46-3)
Synonym: 1,3-dihydroxybenzene, resorcin
Amount in cigarette smoke: TBD

Bottom line

Hydroquinone and **resorcinol** are classified by IARC into Group 3 (not classifiable as to carcinogenicity to humans). However, hydroquinone is suspected to be a kidney carcinogen in animals (rats). Both are not on the Hoffmann's list. But, hydroquinone is listed in proposed regulations by the MA Department of Health. There are no cancer potency factor for hydroquinone and resorcinol. But, hydroquinone is a prioritized candidate chemical under consideration for carcinogenicity evaluation by the California EPA.

Hydroquinone is classified by IARC into Group 3 (unclassifiable as to carcinogenicity to humans) (IARC, 1999)

A cohort of plant workers with definite and lengthy exposure to hydroquinone had low cancer rates compared with two comparison populations; the reason for the lower than expected rates is unclear (Pifer et al., 1995). A cohort of lithographers, some of whom had worked with hydroquinone, had an excess of malignant malignoma based on five cases; but only two of the cases had reported exposure to hydroquinone (Nielsen et al., 1996). Based on these two studies, IARC evaluated human data that there is *inadequate evidence* in humans for the carcinogenicity of hydroquinone. In mice, hydroquinone by oral administration induced hepatocellular adenomas in females only (NTP, 1989), but induced hepatocellular adenomas in another study in males only (Shibata et al., 1991). In rats, it induced renal tubule adenomas in males (NTP, 1989; Shibata et al., 1991). Hydroquinone had no promoting activity in most studies, however, an increase in the multiplicity of esophageal tumors was observed by Yamaguchi et al. (1989) and in the multiplicity of renal cell tumors by Okazaki et al. (1993). IARC evaluated animal data that there is *limited evidence* in experimental animals for the carcinogenicity of hydroquinone.

Resorcinol is classified by IARC into Group 3 (unclassifiable as to carcinogenicity to humans) (IARC, 1999)

The classification was based on animal data, since no case reports or epidemiological studies of cancer in humans were available to the Working Group. Resorcinol was tested for carcinogenicity in one experiment in mice (NTP, 1992) and in one experiment in rats (NTP, 1992) by oral administration. It was also tested in mice by skin application (Stenbaek and Shubik, 1974). No carcinogenic effect was observed in these experiments. In several experiments in rats and hamsters, resorcinol was tested for promoting activity after initiation by known carcinogens. It did not enhance the incidence of tumors of the bladder, forestomach, liver, or kidney. In one study, resorcinol increased the incidence of tongue and esophageal tumors after initiation with N-nitrosomethyl-n-amylamine (Yamaguchi et al., 1989). IARC evaluated animal data that there is *inadequate evidence* in experimental animals for the carcinogenicity of resorcinol.

Hydroquinone and resorcinol are not on Hoffmann's list (Hoffmann, 1993)

Referring to the Hoffmann's table of co-carcinogen (1978), Surgeon General's Report (1981) put a question mark regarding the co-carcinogenic activity of other catechols and phenols.

Hydroquinone is listed in proposed regulations by the MA Department of Health but not resorcinol

EPA has not classified hydroquinone and resorcinol with respect to potential carcinogenicity

There is no cancer potency factor for hydroquinone and resorcinol reported by U.S. EPA (www.epa.gov/iris/subst/indexhtml) and California EPA. However, hydroquinone has been selected as a one of 33 prioritized candidate chemicals under consideration for carcinogenicity evaluation by California EPA (www.oehha.org/prop65/docs_state/bat1crnr.html).

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